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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,898	03/01/2002	Alexander Olek	81658A	4523

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,898	OLEK ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 35-44* is/are pending in the application.

4a) Of the above claim(s) *35-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,43 and 44* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/16/2006 has been entered.

Claim Objections

Claim 14 is objected to because of the following informalities:

Claim 14 recites the limitation of "operatively linked to with unwanted side effects" in line 3 of the instant claim, and should be amended to read as --operatively linked to unwanted side effects--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The previous rejection of claims 1-31 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn in view of amendments made to the instant claims and arguments presented by applicants.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-31, 43, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 43 each recite the limitation "selecting the sites which are differentially methylated" in step (d) of either claim. The antecedent basis for this limitation in the instant claims are unclear as the previous method step (c) recites the limitation of "analyzing the cytosine methylation at chosen sites." As such, it is unclear from the instant claims if "the sites" recited in step (d) refer to the "chosen cites" as recited in step c) or if "the sites" of step (d) is intended to encompass the any differentially methylated site in the DNA of samples A and B. Claims 2-31 and 44 are also included under this rejection due to their dependence from either claim 1 or claim 43.

For the purpose of continuing examination, it has been construed that the limitation "the sites which are differentially methylated" in step (d) of either claims 1 and

43 is limited to the chosen sites of the DNA contained in samples A and B as recited in step (c) of said claims.

Claim 43 recites the limitation of "selecting sites which are differentially methylated between the DNA in biological samples A and B" in step (d) of the instant claim. However, the instant claim recites three separate preparative steps involving samples A and B (steps (a)-(c) of the instant claim) wherein the methylation of DNA in samples A and B is potentially altered. Step (a) involves obtaining a sample (sample A) exposed to at least one drug, chemical substance, and/or pharmaceutical that potentially may effect the methylation of DNA. Step (b) involves obtaining a second sample (sample B) which was not exposed to said at least one drug, chemical substance, and/or pharmaceutical and therefore does not have the same potential alteration to the methylation of DNA in the sample as in sample A. Step (c) is drawn to an analysis step wherein both samples A and B are chemically treated with at least one of bisulfite, hydrogen sulfite or disulfite, which will alter the methylation of DNA in both samples A and B. As such, the DNA of sample A has two methylation states, an initial state effected by at least one drug, chemical substance, and/or pharmaceutical and a second state wherein the DNA is altered by subsequent treatment with at least one of bisulfite, hydrogen sulfite or disulfite. Likewise, sample B has two methylation states, an initial native DNA methylation state from an untreated biological sample and a second state wherein the DNA of the sample is altered by treatment with at least one of bisulfite, hydrogen sulfite or disulfite. It is unclear from the instant claim which or in what

combination these four sample methylation states are used to establish the differential methylation between samples A and B as recited in step (d). Claim 44 is also included under this rejection due to its dependence from claim 43.

For the purpose of continuing examination, it has been construed that step (d) of instant claim 43 drawn to selecting the sites which are differentially methylated between the DNA in biological samples A and B reads on selecting differentially methylated site established between any combination of the above described methylation states of DNA from samples A and B.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 13-21, 23-26, 28, 31, 43, and 44 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Laird et al. (P/N 6,331,393 B1).

The instant claims are drawn to methods for determining the biological effect and/or activity of at least one drug, chemical substance, and/or pharmaceutical composition comprising the steps of obtaining a biological sample A containing DNA,

wherein said sample A was exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, obtaining a biological sample B containing DNA, wherein said sample B was not exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, subsequently analyzing the level of cytosine methylation at chosen sites of the DNA contained in samples A and B, selecting sites which are differentially methylated between the DNA in said samples to generate a knowledge base, and concluding the biological effect of said at least one drug, chemical substance, and/or pharmaceutical composition from said knowledge base.

Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A) (chemical substance) (abstract), as stated in instant claims 1, 9, and 13. Laird et al. disclose methylation amounts in multiple samples are quantitatively determined based on reference to a control reaction (sample B) (col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as recited in instant claims 1 and 43. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as recited in instant claims 1 and 43. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between MLH1 gene

expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2 graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (col. 24, lines 48-67). Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (col. 1, lines 14-17) which represents cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite (col. 5, lines 19-20 and 31), as recited in claim 44. Laird et al. disclose various methods to identify altered methylation sites in cancer cells (col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal mucosa (healthy) tissue samples (Figures 7 and 8; col. 22, lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of

bisulfite-treated DNA samples (col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue in all normal and tumor samples (col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites that are located in methylation relevant genes associated with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sites of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA samples are analyzed by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Laird et al. disclose that altered DNA methylation pattern of cytosine residues is mutagenic (col. 2, lines 34-36) which demonstrates that the colorectal samples mentioned above represent genes associated with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen) (col. 23, lines 28-37) which represents histologically, dissected biological material from

healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (col. 9, lines 42-46). Laird et al. disclose using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (col. 14, lines 5-20) which represent selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as stated in instant claims 20, 26, and 31.

Response to Arguments

Applicant's arguments filed 02/16/2006 have been fully considered but they are not persuasive.

In regards to the rejection of claims as being anticipated by Laird et al., applicants argue that instant claim 1 requires (i) that biological sample A be exposed to the drug, chemical and/or pharmaceutical composition, (ii) that biological sample B not be exposed to the drug, chemical and/or pharmaceutical composition, and (iii) that after said exposure or non-exposure, the level of cytosine methylation in biological samples A and B be analyzed.

In response, it is reiterated from the above rejection that Laird et al. discloses a method for determining cytosine methylation patterns in genomic DNA after being treated with sodium bisulfite, contacting a DNA sample from a patient with a modifying agent, (i.e. sodium bisulfate), and quantitatively determining DNA methylation patterns based on reference to a control reaction representing an unexposed biological sample. As such, applicant argument fails to point out the patentable novelty of the claimed

invention over the state of the art disclosed by the cited reference on which the rejection is based.

In regards to newly presented claims 43 and 44, applicants argue that Laird et al. does not teach or suggest obtaining a biological sample A that was exposed to at least one drug, chemical substance and/or pharmaceutical composition, obtaining a biological sample B that was not exposed to said at least one drug, chemical substance and/or pharmaceutical composition, and then analyzing the level of cytosine methylation at chosen sites of the DNA contained in the biological samples A and B, wherein said analyzing comprises chemically treat each of said biological samples A and B with at least one of bisulfite, hydrogen sulfite or disulfite.

In response, it is noted that Laird et al. discloses the collection and preparation of multiple biological samples from a patient, treating said samples with sodium bisulfate, and analyzing the methylation patterns of genomic DNA from said patient samples. In the instant case, the disclosed treatment of a patient sample with sodium bisulfate reads on the instantly claimed limitations of exposing a sample to at least one drug, chemical substance and/or pharmaceutical composition as well as treating said sample with at least one of bisulfite, hydrogen sulfite or disulfite. Further, the disclosed procedures also set forth obtaining an untreated biological sample (sample B) and subsequently treating said sample with at least one of bisulfite, hydrogen sulfite or disulfite.

Conclusion

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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